Antiviral agents for hepatitis B virus-related cirrhosis (Protocol)

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[Intervention Protocol]

Antiviral agents for hepatitis B virus-related cirrhosis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To compare the benefits and harms of different antiviral regimens in patients with HBV-related liver cirrhosis.

BACKGROUND

Description of the condition

Chronic hepatitis B virus (HBV) infection is a serious health problem because of its worldwide distribution and its potential adverse sequelae, including cirrhosis, hepatocellular carcinoma, and death (Lavanchy 2004). It is estimated that each year, worldwide, more than 200,000 people, chronic carriers of HBV, die of liver cirrhosis, and more than 300,000 people, chronic carriers of HBV, die of hepatocellular carcinoma (Perz 2006). Since HBV replication, defined as the presence of hepatitis B e antigen (HBeAg) or HBV deoxyribonucleic acid (DNA) more than 2000 international units (IU)/mL in the blood, or both, may persist after the development of cirrhosis, liver disease may continue to progress, and hepatic decompensation or hepatocellular carcinoma may occur (Chen 2007). Hepatic decompensation usually presents with at least one episode of ascites, jaundice, hepatic encephalopathy, or variceal bleeding (De Jongh 1992).

An estimated 15% to 40% of untreated patients with chronic HBV infection may develop cirrhosis, liver failure, hepatocellular carcinoma, or a combination of these (Lavanchy 2004). The aim of anti-viral therapy in these patients is to prevent the development of cirrhosis and its associated complications, in an effort to improve patient survival and quality of life (Belongia 2008). However, patients with decompensated HBV cirrhosis at initial presentation have a poor short-term prognosis with an estimated five-year survival of only 14% (De Jongh 1992). Although liver transplantation is an effective treatment option for decompensated HBV cirrhosis, the ongoing shortage of donor organs and limited availability of this resource worldwide precludes the majority of HBV patients in endemic areas from undergoing transplantation (Liaw 2008).

Seven drugs are currently approved for the management of chronic HBV infection: standard interferon, lamivudine, adefovir, entecavir, pegylated interferon-alpha (peginterferon-alpha), telbivudine, and tenofovir (Lok 2009). Interferons enhance host immunity against HBV-infected hepatocytes but have a number of dose-dependent adverse effects including neuropsychiatric toxicity and myelotoxicity, which preclude their safe use in patients with advanced HBV (Lok 2009). Interferon was not only poorly tolerated in patients with decompensated HBV cirrhosis but also

associated with disease flares and worsening liver disease status (Perrillo 1995). In contrast, oral anti-viral agents have a generally favourable adverse effect profile and are well tolerated in patients with compensated as well as decompensated HBV (Liaw 2004). In addition, these agents can directly and rapidly inhibit HBV replication and lead to improvement in hepatic necro-inflammation, serum alanine aminotransferase levels, and global liver function even in patients with advanced disease (Liaw 2004). All of these antivirals are competitive inhibitors of the HBV DNA polymerase via competition with the incorporation of the natural endogenous intracellular nucleotides in nascent HBV DNA and cause DNA chain termination. Furthermore, all of these nucleoside analogues have activities conferring biochemical, virological, and serological improvement in patients with chronic hepatitis B (Lok 2009; EASL 2012; Liaw 2012). Nucleoside analogues can also retard the progression of fibrosis and reverse fibrosis and cirrhosis (Dienstag 2003; Hadziyannis 2006; Chang 2010). Long-term therapy may also prevent hepatic decompensation in patients with advanced fibrosis and cirrhosis (Liaw 2004). The generally favourable adverse effect profiles of lamivudine, adefovir, entecavir, telbivudine, and tenofovir, coupled with the low rates of anti-viral drug resistance with newer agents such as entecavir, which had the lowest rate of drug resistance in treatment-naive patients with HBeAg-positive chronic hepatitis B, make them attractive for use beyond one year. However, infrequent but serious adverse events such as myopathy, neuropathy, and pancreatitis as well as reversible renal impairment have been reported during post-marketing surveillance (Keeffe 2006; Lok 2007).

The Child-Turcotte-Pugh (CTP) score and model for end-stage liver disease (MELD) score are the two liver-specific scoring systems that have been used to assess disease severity in patients with cirrhosis. The CTP score was originally developed to predict post-operative mortality in bleeding patients with alcoholic liver cirrhosis undergoing portal-systemic shunt surgery (Pugh 1973). Although it predicts one-year survival and post-surgical risks of complications, it does not predict short-term mortality (Schuppan 2008). The MELD score was initially developed to predict short-term mortality in patients undergoing transjugular intrahepatic portosystemic shunting (Malinchoc 2000). It was later used to predict three-month mortality in patients with cirrhosis, irrespective of cause, and has been adopted to prioritise organ allocation for liver transplantation in the United States since 2002 (Kamath 2001; Wiesner 2003). A major feature of the MELD scoring system is the inclusion of renal function in the model. Renal dysfunction commonly occurs during the course of disease progression in cirrhosis and has been shown to have a detrimental prognostic impact on survival (Fernandez 2001).

Description of the intervention

Oral antiviral agents for treatment of HBV, such as lamivudine, adefovir, entecavir, telbivudine, and tenofovir, are chemically modified analogues of naturally occurring nucleosides or nucleotides that pharmacologically inhibit the polymerase activity of HBV, leading to reduced viral replication and decreases in serum HBV DNA levels.

How the intervention might work

Antiviral agents could improve a patient's quality of life and decrease the progression to liver cirrhosis and chances of developing hepatocellular carcinoma as well as the risk of death.

Why it is important to do this review

Although antiviral agents seem to be beneficial for patients with HBV-related cirrhosis, these drugs have a warning because of their potential for inhibition of human DNA polymerase gamma involved in mitochondrial DNA replication. A reduction in intracellular mitochondrial DNA levels can lead to varying clinical manifestations of mitochondrial toxicity in long-term treatment. So, there is no clear safety profile of the nucleoside analogues when given alone or in combination for prolonged periods of time. This review aims to provide evidence of the beneficial and harmful effects of treatment with antiviral agents in patients with HBV-related liver cirrhosis.

There are currently two Cochrane systematic review protocols that concentrate on chronic hepatitis B. Whitfield 2010 is evaluating the beneficial and harmful effects of levamisole for patients with chronic hepatitis B while Zhao 2010 is evaluating the effects of telbivudine for chronic hepatitis B.

To date, no systematic review has been conducted on the benefits and harms of antiviral agents for liver cirrhosis related to hepatitis B and their effect on progression of cirrhosis and developing of hepatocellular carcinoma.

OBJECTIVES

To compare the benefits and harms of different antiviral regimens in patients with HBV-related liver cirrhosis.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider all randomised clinical trials that assess antiviral intervention in patients with HBV-related cirrhosis. We will use

non-randomised clinical studies retrieved with the searches for randomised trials for extraction on data on harm only.

Types of participants

Adults at the age of 18 years or above, of either sex, who have been diagnosed with HBV-related cirrhosis. Diagnosis of HBV should have been based on the presence of detectable HBV DNA by a DNA hybridisation method or polymerase chain reaction, and the cirrhosis should be related to the HBV.

Criteria for the diagnosis of cirrhosis should be patients with definite diagnosis of cirrhosis based on liver biopsy or laboratory, radiographic, or Fibro scan findings compatible with the diagnosis of cirrhosis.

The randomised clinical trials should have included participants with compensated or decompensated HBV-related liver cirrhosis. We will exclude chronic HBV patients who do not have developed cirrhosis, patients with liver cirrhosis unrelated to HBV, patients with liver cirrhosis with combined HBV and HCV, and those with hepatocellular carcinoma.

Types of interventions

The experimental intervention will be antiviral drugs against HBV as monotherapy (lamivudine, adefovir dipivoxil, entecavir, telbivudine, or tenofovir disoproxil fumarate) at any dose and minimum duration of six months, or a combination of these antiviral agents. We will compare one intervention versus placebo, no treatment, or another antiviral treatment.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Hepatic-related mortality.
3. Non-fatal serious adverse events: serious adverse events are defined according to the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (ICH-GCP 1997), as any event that is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, and any important medical event, which may have jeopardised the patient or requires intervention to prevent it.
4. Quality of life (using standardised objective scales: i.e., Health Day Measures questionnaire, Short-form Health Survey, Manchester Short Assessment of Quality of Life, EQ-5D, World Health Organization (WHO)-Quality of life BREF, etc.)

Secondary outcomes

1. Number of patients without improvement of cirrhosis progression by MELD score according to CTP score.
2. Number of patients who developed hepatocellular carcinoma.
3. Number of patients with non-serious adverse events.

Search methods for identification of studies

Electronic searches

We will search The Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2013), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and Science Citation Index Expanded (including Conference Proceedings Citation Index-Science) (Royle 2003). The search strategies for each database with the expected time spans of the searches are listed in Appendix 1. If needed, we will improve the searches at the review stage.

Searching other resources

Abstracts from the European Association for the Study of Liver disease (EASL) published in *Journal of Hepatology* and from the American Association of Study of Liver Disease (AASLD) published in*Hepatology* will be obtained through The Cochrane Hepato-Biliary Group Controlled Trials Register.

Data collection and analysis

Selection of studies

We will assess the titles and abstracts of records retrieved from the search by using at least two review authors in order to reduce the possibility that relevant reports are discarded. We will evaluate titles and abstracts to remove obviously irrelevant reports and will merge search results in order to remove duplicate records of the same report. Then, we will retrieve full text of the potentially relevant reports. We will also examine full-text reports for compliance of studies with eligibility criteria. If it is necessary, we will correspond with investigators, where appropriate, to clarify study eligibility and request further information, such as missing results. The review authors will independently select studies to be included in the review. We will include a list of excluded studies with giving the primary reasons for the exclusions. Wherever disagreement occurs, we will generally resolve it by discussion or by asking arbitration by another person.

Data extraction and management

We will include studies with some characteristics such as:

- Details of participants: age (mean (standard deviation)), sex (%), number of patients randomised; inclusion and exclusion criteria, ethnicity, sociodemographic details (e.g., education level) and the presence of co-morbid conditions.
- Details of trial: timing of the studies, the settings of studies, and funding of the trials; trials design; length of follow-up; use of intention-to-treat analysis; and publication status.
- Details of Interventions: routes of delivery, doses, length of treatment, of additional intervention(s), and a different regimen of treatment, placebo or no treatment in the control group.
- Criteria for the diagnosis of cirrhosis will be patients with definite diagnosis with liver biopsy or laboratory, radiographic, or Fibro scan findings compatible with the diagnosis of cirrhosis.
- Details of outcome: definition, unit of measurement, number of mortality, non-fatal serious adverse events, serious adverse events, life-threatening events, disabilities, and any important medical events, and quality of life.

We will design the data collection forms and will record the name (or identification number) of the person who is completing the forms. We will also include assessment (or verification) of eligibility of the study for the review. At least two review authors will independently extract data from every report to minimise errors and reduce potential biases being introduced by review authors. We will pilot test all forms using a representative sample of the studies to be reviewed. Where disagreement occurs, it will be resolved by discussion among the review authors (at first step) or by arbitration by another person, or by contacting the study authors.

Assessment of risk of bias in included studies

We will follow the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and The Cochrane Hepato-Biliary Group Module (Gluud 2013). We will define methodological quality as the confidence that the design and the report of the randomised clinical trial would restrict bias in the comparison of the intervention (Moher 1998). According to empirical evidence (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Higgins 2011; Lundh 2012; Savović 2012; Savović 2012a), the methodological quality of the trials, hence risk of bias, will be assessed as follows:

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Uncertain risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Uncertain risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants, personnel, and outcome assessors

- Low risk of bias: blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding.
- Uncertain risk of bias: there was insufficient information to assess whether blinding was likely to induce bias on the results.
- High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes were likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, were employed to handle missing data.
- Uncertain risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: all outcomes were pre-defined and reported, or all clinically relevant and reasonably expected outcomes were reported.
- Uncertain risk of bias: it is unclear whether all pre-defined and clinically relevant and reasonably expected outcomes were reported.
- High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported, and data on these outcomes were likely to have been recorded.

For a trial to be assessed with low risk of bias in the selective outcome reporting domain, the trial should have been registered on the www.clinicaltrials.gov website or a similar register, or there should be a protocol (e.g., published in a paper journal). In the case when the trial was run and published in the years when trial registration was not required, we will carefully scrutinise all publications reporting on the trial to identify the trial objectives and outcomes. If usable data on all outcomes specified in the trial objectives were provided in the publications results section, then the trial can be considered a low risk of bias trial in the 'Selective outcome reporting' domain.

For-profit bias

- Low risk of bias: the trial appears to be free of industry sponsorship or other type of for-profit support that may manipulate the trial design, conductance, or results of the trial.
- Uncertain risk of bias: the trial may or may not be free of for-profit bias as no information on clinical trial support or sponsorship was provided.
- High risk of bias: the trial was sponsored by the industry or has received other type of for-profit support.

Other bias

- Low risk of bias: the trial appears to be free of other components (e.g. academic bias) that could put it at risk of bias.
- Uncertain risk of bias: the trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias: there are other factors in the trial that could put it at risk of bias (e.g. authors have conducted trials on the same topic, etc.).

We will consider trials assessed as having 'low risk of bias' in all of the above specified individual domains as trials with 'low risk of bias'. We will consider trials assessed as having 'uncertain risk of bias' or 'high risk of bias' in one or more of the specified individual domains as trials with 'high risk of bias' .
If disagreements among review authors' evaluation occur, we will resolve them by discussion.

Measures of treatment effect

We will use the software package Review Manager 5 provided by The Cochrane Collaboration (RevMan 2012).

Dichotomous data

The effect measures of choice are risk ratio or risk difference or both, and number needed to treat for an additional beneficial outcome (NNTB) with 95% confidence interval (CI), using both fixed-effect and random-effects meta-analysis models. Risk ratio calculations do not include trials in which no events occur in the groups, whereas risk difference calculations do. This is why we plan to report the results of both effect measures if the conclusions reached at differ due to the trials with zero events in the groups.
P values of all trials will be calculated based on the Mantel-Haenszel method. The Review Manager 5 software automatically adds 0.5 to each cell of the 2 x 2 table for any study with zero events (e.g. no events in one group) (RevMan 2012), so the problems with computation of estimates and standard errors will be eliminated. Mantel-Haenszel methods have better statistical properties when there are few events.

Continuous data

We will present the results as mean differences (MD) with 95% CI using the fixed-effect and random-effects models. P values of all trials will be calculated based on the generic inverse variance. When pooling data across trials, we will estimate the MD if the outcomes are measured in the same way between trials. We will use the standardised mean difference (SMD) to combine trials that measure the same outcome but use different methods. If it is only one trial that provides data on an outcome specified in the protocol, meta-analyses will not be possible, and we will report and discuss this in the review.

Time to event data

We will analyse time-to-event data as dichotomous data using a fixed time point, so the proportion of patients who have incurred the event before the time point will be known for both groups. We will then construct a 2 x 2 table, and we will express treatment effects as risk ratios, odds ratios, or risk differences.
When overall results are statistically significant by both fixed- and random-effects models, we will calculate the relative risk reduction (RRR), NNTB, and the number needed to treat for an additional harmful outcome (NNTH).

Unit of analysis issues

The unit of analysis will be the patients recruited into the trial.
We will include simple parallel randomised clinical trials, as well as cluster randomised trials and cross-over trials, in the meta-analyses. We will identify any cluster-randomised trials that will be included for the review, but we will not combine these with individually randomised trials in the same meta-analysis (i.e. they will be analysed separately). We will meta-analyse effect estimates and their standard errors from correct analyses of cluster-randomised trials using the generic inverse-variance method in Review Manager 5 (RevMan 2012). Care will be taken to avoid 'unit of analysis' errors when analysing these types of trials (Higgins 2011).
The cross-over trial is not a suitable method for the condition and intervention in our question because the intervention (i.e. antiviral agents) could have a lasting effect that compromises entry to subsequent periods of the trial. In the presence of carry-over,

we will include only data from the first period of a cross-over trial in the meta-analysis. The first period of a cross-over trial is in fact a parallel group comparison. So, in case of cross-over studies, we will follow the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* on how to deal with data from cross-over studies (Higgins 2011). We will also perform sensitivity analysis with inclusion of only simple parallel randomised clinical trials in the meta-analysis.

Dealing with missing data

We will contact study authors for data that were measured but not reported. We will perform all analyses according to the intention-to-treat method, including all participants irrespective of compliance or follow-up. Regarding the four primary outcomes, we will include patients with incomplete or missing data in the sensitivity analyses by imputing them according to the following two extreme scenarios (Hollis 1999; Gluud 2013):

- Extreme case analysis favouring the experimental intervention ('best-worse' case scenario): none of the drop-outs/participants lost from the experimental arm, but all of the drop-outs/participants lost from the control group experienced the outcome, including all randomised participants in the denominator.
- Extreme case analysis favouring the control ('worst-best' case scenario): all drop-outs/participants lost from the experimental arm, but none from the control arm experienced the outcome, including all randomised participants in the denominator.

Assessment of heterogeneity

We will formally test for statistical heterogeneity using the Chi^2 test for statistical homogeneity with a P value < 0.1 set as the cut-off. The impact of any statistical heterogeneity will be quantified using the I^2 statistic (Higgins 2011).
We will interpret the I^2 value as:

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We will assess publication bias by looking for funnel plot asymmetry if there are at least 10 included trials (Egger 1997).

Data synthesis

We will perform the meta-analyses using the software package Review Manager 5 (RevMan 2012), and following the recommendations of The Cochrane Collaboration (Higgins 2011), and The Cochrane Hepato-Biliary Group Module (Gluud 2013). We will use both random-effects model (DerSimonian 1986) and fixed-effect model (DeMets 1987) meta-analyses. We will use the generic inverse variance method in Review Manager 5 (Higgins 2011; RevMan 2012). In case of discrepancy in the results of two models, we will present the results using both methods. If there is no statistically significant difference in the results, then we will present the results using the fixed-effect model.
If the data are not available for meta-analyses or if meta-analyses are considered an inappropriate tool for the included trials, we will attempt to present the data of such outcomes in a descriptive way.
Trial sequential analysis
Trial sequential analysis (TSA) is a tool for quantifying the statistical reliability of the data in a cumulative meta-analysis (CTU 2011; Thorlund 2011), controlling for random errors due to sparse data and repetitive testing on accumulating data (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009, Wetterslev 2009; Thorlund 2010; Thorlund 2011a). TSA is a methodology that combines a required information size calculation (cumulated sample sizes of trials to prove or disprove a certain intervention effect) with the threshold of statistical significance. We will base our calculations on the diversity-adjusted required information size for dichotomous outcomes on the proportion of patients with the outcome in the conventional group, a RRR of 20%, an alpha (type I error) of 5%, a beta (type II error) of 20% (power 80%), and the diversity of the meta-analysis (Wetterslev 2009). We may perform sensitivity analyses choosing other variables.

Subgroup analysis and investigation of heterogeneity

We plan to perform subgroup analyses on the following items:

- Trials with low risk of bias compared to trials with high risk of bias.
- Trials with co-interventions compared to the trials without co-interventions.
- Patients co-infected with HIV compared to patients without co-infection.
- Cirrhosis progression at entry into the trial; comparing the interventions effects in trials with compensated cirrhosis to the ones with decompensated cirrhosis.
- Trials without losses to follow-up compared to trials with losses to follow-up.
- Trials published as full paper articles compared to trials published as abstracts only.

Sensitivity analysis

We will exclude from the meta-analyses the trials in which allocation concealment was not described or was likely to be known to the investigators who assigned the participants.
We will conduct 'best-worst' and 'worst-best' case scenario analyses as already described in Dealing with missing data.

Summary of findings' tables

We will summarise the evidence on all binary outcomes in a 'Summary of findings' table, using GRADEpro (ims.cochrane.org/revman/other-resources/gradepro).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at review stage.	((antiviral and (drug* or agent*)) or lamivudine or adefovir dipivoxil or entecavir* or telbivudin* or tenofovir*) AND (hepatitis B or hep B or hbv) AND (cirrho* or fibro*)
Cochrane Central Register of Controlled Trials (CENTRAL)	Latest issue.	#1 MeSH descriptor: [Antiviral Agents] explode all trees #2 (antiviral and (drug* or agent*)) or lamivudine

(*Continued*)

		or adefovir dipivoxil or entecavir* or telbivudin* or tenofovir* #3 #1 or #2 #4 MeSH descriptor: [Hepatitis B] explode all trees #5 hepatitis B or hep B or hbv #6 #4 or #5 #7 MeSH descriptor: [Liver Cirrhosis] explode all trees #8 cirrho* or fibro* #9 #7 or #8 #10 #3 and #6 and #9
MEDLINE (Ovid SP)	1946 to the date of search.	1. exp Antiviral Agents/ 2. ((antiviral and (drug* or agent*)) or lamivudine or adefovir dipivoxil or entecavir* or telbivudin* or tenofovir*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 3. 1 or 2 4. exp Hepatitis B/ 5. (hepatitis B or hep B or hbv).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 6. 4 or 5 7. exp Liver Cirrhosis/ 8. (cirrho* or fibro*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 9. 7 or 8 10. 3 and 6 and 9 11. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 12. 10 and 11
EMBASE (Ovid SP)	1974 to the date of search.	1. exp antivirus agent/ 2. ((antiviral and (drug* or agent*)) or lamivudine or adefovir dipivoxil or entecavir* or telbivudin* or tenofovir*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device

(*Continued*)

		trade name, keyword] 3. 1 or 2 4. exp hepatitis B/ 5. (hepatitis B or hep B or hbv).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 6. 4 or 5 7. exp liver cirrhosis/ 8. (cirrho* or fibro*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 9. 7 or 8 10. 3 and 6 and 9 11. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 12. 10 and 11
Science Citation Index Expanded	1900 to the date of search.	#5 #4 AND #3 AND #2 AND #1 #4 TS=(random* or blind* or placebo* or meta-analys*) #3 TS=(cirrho* or fibro*) #2 TS=(hepatitis B or hep B or hbv) #1 TS=((antiviral and (drug* or agent*)) or lamivudine or adefovir dipivoxil or entecavir* or telbivudin* or tenofovir*)

WHAT'S NEW

Date	Event	Description
22 May 2014	Amended	The letter 'h' was omitted in the name of the third author, Khatereh Isazadehfar

CONTRIBUTIONS OF AUTHORS

EA: drafted and revised the protocol.

LE: contributed to the protocol.

KI: contributed to the protocol.

All authors agreed on the final protocol version.

DECLARATIONS OF INTEREST

None known.